REMARKS

Formal Matters

Claims 136-154 and 156-157 are pending after entry of the amendments set forth herein.

Claims 136-140, 144-147, 156 and 157 are amended for clarity. Claims 158 and 159 are new, support for which is found at pages119 to 121. No new matter has been added.

Claim 155 is cancelled without prejudice.

Reconsideration of this application is respectfully requested.

Request for Rejoinder

The Examiner's decision to make the Restriction Requirement of September 9, 2009, final is noted.

A Petition to the Director under 37 CFR § 1.181 requesting review of the Restriction Requirement will be filed in due course.

Drawings

The Examiner notes that the specification refers to drawings, and that no drawings appear to be on the record.

However, Applicants own records are confirmed by PAIR in that the drawings for this case are included as pages 165 to 171 of a document entitled "Documents submitted with 371 Applications", which document was filed in this case on December 16, 2005, i.e., the day on which the application was filed in the U.S.

The Applicants therefore believe that drawings are on record in the case, and no drawings need be provided.

Acknowledgement of such is respectfully requested.

Rejection of claims under 35 U.S.C.§ 112, first paragraph

Claims 136-143 and 155-157 are rejected as not meeting the written description requirement of 35 U.S.C. § 112, first paragraph. This rejection is respectfully traversed.

In making this rejection, the Examiner argues that there is no nexus between steps (b) and (c) of claim 136 and, as such, the claimed method is inadequately described.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, Applicants have amended claim 136 to clarify the nexus between the two determining steps of the claim.

The Applicants submit that this rejection has been adequately addressed and, as such, this rejection may be withdrawn. Withdrawal of this rejection is therefore requested.

Rejection of claims under 35 U.S.C. § 112, first paragraph

Claims 136-143 and 155-157 are rejected as not meeting the enablement requirement of 35 U.S.C. § 112, first paragraph.

In making this rejection, the Examiner argues that variants of SEQ ID NO:2 are not enabled because "it is unpredictable whether a GPCR that has 95% sequence identity to SEQ ID NO: 2 shares the same property of RUP40 GPCR of SEQ ND NO:2 because the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of GPCR variants and homologs. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function". Applicants traverse.

The specification discloses the sequence of human RUP40 (SEQ ID NO:2), as well as the sequence of rat RUP40 (SEQ ID NO:4) and mouse RUP40 (SEQ ID NO:6). See ¶14 on page 4. The specification provides guidance for making constitutively active mutants of RUP40. See ¶68 on page 18. Specific allelic variants of human RUP40 are described in ¶69 on page 18, and in the sequence listing. RUP40 fusion proteins are described throughout the specification. See, e.g., pages 95-97. The specification also teaches that several techniques for making variants, e.g., by site-directed mutagenesis, PCR or direct synthesis, were generally available at the time of filing. See ¶390 on page 80 and ¶¶410 and 411 on page 90. The specification states that RUP40 is a GPCR that is coupled to Gq and increases the production of IP_3 when stimulated. See, e.g., ¶14 on page 4, ¶553 on page 133 and Fig. 5. The specification describes the general structure/function relationship of GPCRs. See, e.g, ¶5

on page 2 to ¶13 on page 4. The specification describes a variety of methods for assaying GPCRs which can be used to test variant proteins for activity. See the section starting on page 93 as well as page 132. The specification also describes a working example of a cell hypertrophy assay that employs RUP40, as well as a gene expression assay to assay ANF, which is induced by RUP40. See, Example 15 on page 133.

Moreover, the record shows that RUP40 is a member of an extremely well characterized family of proteins: the GPCRs. A search of NCBI's PubMed database reveals that there are well over 3700 journal articles, including 614 reviews, that have a publication date that precedes the priority date of the instant application (June 20, 2003) and contain the phrase "GPCR" OR "G protein-coupled receptor" in the abstract. See Exhibit A. Thus, at the priority date of the instant application, GPCR proteins were a subject of significant interest in the scientific community, and the level of skill in the art was very high. The art in which the subject RUP40 protein belongs was therefore highly developed at the priority date of the instant application. For example, at the priority date of the instant application one of skill in the art would have knowledge of the atomic coordinates of at least one GPCR (see, e.g., reference A listed on Exhibit B). At the time of filing, the structure/function relationship of many GPCRs had been investigated (see, e.g., references B-H listed on Exhibit B), and several reviews on the structure/function relationship of GPCRs had been published (see, e.g., references I-O listed on Exhibit B). In addition, at the time of filing, one of skill in the art would have been aware of several algorithms for predicting GPCR structure (see, e.g., references P and Q listed on Exhibit B), an algorithm for predicting important residues in GPCRs (see, e.g., reference R listed on Exhibit B), and reviews on the engineering of GPCRs by domain swapping (see, e.g., references S and T listed on Exhibit B). The references listed in Exhibit B are cited in an Information Disclosure Statement filed herewith.

Given the information in the instant specification and the deep general understanding of the structure and function of GPCR proteins, the Applicant submits that one of skill in the art would be make and use a large number of operable variants of RUP40 without undue experimentation.

Furthermore, claim 136, from which all rejected claims depend, is directed to a screening method that employs a G protein-coupled receptor (GPCR) comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2. Importantly, claim 136 also requires "determining that the compound inhibits *signaling by said G protein-coupled receptor*" (emphasis added). As such, the only variants of the recited sequence that are encompassed by the claim are variants that are capable of signaling. Non-functional variants are excluded from the claims as written. The rejected claims therefore require a GPCR that is both structurally *and* functionally defined.

Given that the GPCR recited in the rejected claims is structurally *and* functionally defined, one of skill in the art would have no trouble identifying a GPCR that could be used in the claimed method given what is disclosed in the specification and what was known in the art at the time of filing. The Examiner's contention that "it is unpredictable whether a GPCR that has 95% sequence identity to SEQ ID NO: 2 shares the same property of RUP40 GPCR of SEQ ND NO:2" is moot in view of the foregoing discussion.

Moreover, predictability is but one of the factors in the Wand's analysis. The crux of the question of enablement is whether, taking all the Wand's factors into account, practice of the claimed method would require undue experimentation.

The law relating to enablement is well established.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993)

> "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not

> preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive'".

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of hot to practice a desired embodiment of the invention claimed.

PPG Indus., 75 F.3d 1564 (quoting *Ex parte Jackson* 217 USPQ 804 807 (BPAI 1982))

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1998).

The Applicants' arguments for withdrawal of the outstanding rejection are consistent with *Ex parte Kubin* (BPAI 2007; Appeal no. 2007-0819) which is a *precedential* decision by the BPAI. The grounds of the enablement rejection decided in *Ex parte Kubin* are similar to the grounds of rejection in the instant case in that in *Ex parte Kubin* a claim reciting "80% identity" language[1] was rejected as being non-enabled because there were no working examples other than SEQ ID NOS:1 and 2, and because very small changes in sequence,

[1] Claim 73, the independent claim discussed in *Ex parte Kubin* recites: "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48".

even one amino acid, can alter protein function. In this case, the Board acknowledged that although biotechnology is unpredictable, the other Wands factors, particular "the state of the art" and "the relative skill of those in the art" weigh more heavily in the Applicants' favor. In essence, the Board in *Ex parte Kubin* stated that "The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art". Given the evidence described above and applying the logic of *Ex parte Kubin*, the Applicants submit that practice of the claimed method would not require undue experimentation, and this rejection should be withdrawn.

The Applicants also note that the BPAI has reversed several rejections based on similar grounds to those of this rejection. For example, in *Ex parte Liao* (BPAI 2008; Appeal No. 2008-4364) the claims[2] were rejected because the specification did not identify any domain of EDG-1 that was critical for EDG-1 activity. Like RUP40, EDG-1 is a GPCR. In this case, the Board recognized that the effect of amino acid substitutions can be unpredictable. However, the rejection was reversed because although one of skill in the art might have been required to make and test every EDG1 variant encompassed by the claims, the claims were nevertheless enabled because the level of skill in the art is high (particularly because EDG-1 is a GPCR) and the experimentation would have been routine. Likewise, in *Ex parte Heck* (BPAI 2008; Appeal No. 2008-2875[3]), the Board noted that "some deletions and mutations will reduce activity". However, the Board reversed the rejection because "the amount of experimentation to practice the full scope of the claimed invention might be extensive, such experimentation would have been routine." Similarly, in *Ex parte Abad* (BPAI 2007; Appeal No. 2007-4356[4]), the Board again noted "any particular mutation in a protein sequence, even a conservative mutation, may result in an unpredictable change in the

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[2] The claims appeal in this case were directed to a screening method that employed a polypeptide "having at least 95% identity to an amino acid sequence of SEQ ID NO:5".

[3] The claims appeal in this case were directed to an isolated polynucleotide that is "at least about 98% identity" to SEQ ID NO:1.

[4] The claims appeal in this case were directed to an isolated nucleotide acid "having at lest 90% sequence identity to" SEQ ID NO:3, wherein the sequence encodes a pesticidal polypeptide.

activity or function of a particular protein". In this case, the Board reversed the rejection because identifying active variants "would have required some experimentation in order to determine which nucleic acids would have pesticide activity and against which pests, but that experimentation would have been routine, not undue".

The Applicants understand that every case has its own set of facts that distinguishes that case from others. However, given the guidance in the instant specification, the vast amount of structural information on GPCRs available in the prior art, the similarity of this case to the cases discussed in *Ex Parte Kubin*, *Ex parte Liao*, *Ex parte Heck* and *Ex parte Abad*, and the limited scope of the claims, which recite structural and functional parameters for the sequences used in the claimed method, the Applicants believe that one of skill in the art would be able to practice the claimed method without undue experimentation. As such, this rejection should be withdrawn.

The Examiner is requested to reconsider this rejection in view of the foregoing discussion.

Finally, in the Office Action, the Examiner contends that "without a known ligand/agonist, one skilled in the art would not be able to identify an antagonist of the human RUP40 that inhibits hypertrophy in the heart" (see OA, page 6) and "an activator (agonist) of the receptor would not be able to in inhibit hypertrophy in the heart" (see OA, page 7). The Examiner provides no evidence to support these statements.

The Applicants initially note that the claimed method is not limited to a method for identifying antagonists. Rather, the claims are directed to a method for identifying *inhibitors* of the recited GPCR, which includes, for example, inverse agonists as well as antagonists.

Moreover, Example 15 on page 133 of the instant specification presents experimental evidence showing that overexpression of *wild type* RUP40 stimulates hypertrophy of cardiomyocytes in the absence of a known ligand or agonist. The Examiner's argument that a known ligand or agonist is required to identify an antagonist of the human RUP40 is therefore inconsistent with the data shown in the instant application, and carries no weight.

Withdrawal of this rejection is therefore rejected.

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 136-143 and 155-157 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed.

Claim 136 is rejected as being indefinite because it is allegedly unclear what is being modulated in the phrase "determining the ability of the compound to modulate said G protein-coupled receptor".

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, Applicants have claim 136 to recite "determining that the compound to inhibits signaling by said G protein-coupled receptor".

The Applicants submit that this aspect of the rejection has been addressed.

Claim 136 is further rejected as being indefinite because there is allegedly a gap between the steps. In explaining the rejection, the Examiner states that the claim lacks a description of "how to determine the ability of a compound to modulate the G protein-coupled receptor; and how to determine is [sic] said compound has an activity that inhibits hypertrophy in the heart."

Without any intention to acquiesce to the correctness of this rejection, Applicants have amended claim 136. It is believed that this aspect of the rejection has been addressed.

Finally, claim 155 is rejected because the claim appears to broaden an element of claim 136, from which claim 155 depends.

Claim 155 is cancelled and, as such, this rejection is moot. Withdrawal of this rejection is requested.

Claim objections

The claims are objected to because they recite non-elected species (i.e., species other than hypertrophic cardiomyopathy).

The Applicants kindly request rejoinder of the non-elected species upon allowance of claim 132.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-060.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: November 30, 2009

By: /James S. Keddie, Reg. No. 48,920/
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Enclosures: Exhibit A from AREN-060
Exhibits B from AREN-027
IDS to cite refs from Exhibit B

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Exhibit A

PubMed

("1980/01/01"[Publication Date] : "2003/06/20"[Publication Date]) AND (GPCR

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1. Ligand characterization using microphysiometry.
   Pitchford S.
   Curr Protoc Neurosci. 2001 May;Chapter 7:Unit7.8.
   PMID: 18428534 [PubMed - indexed for MEDLINE]

2. The substituted-cysteine accessibility method (SCAM) to elucidate membrane protein structure.
   Liapakis G, Simpson MM, Javitch JA.
   Curr Protoc Neurosci. 2001 May;Chapter 4:Unit 4.15.
   PMID: 18428478 [PubMed - indexed for MEDLINE]

3. Constitutively signaling g-protein-coupled receptors and human disease.
   Arvanitakis L, Geras-Raaka E, Gershengorn MC.
   Trends Endocrinol Metab. 1998 Jan-Feb;9(1):27-31.
   PMID: 18406231 [PubMed - in process]

4. New aspects of g-protein-coupled receptor signalling and regulation.
   Milligan G.
   Trends Endocrinol Metab. 1998 Jan-Feb;9(1):13-9.
   PMID: 18406229 [PubMed - in process]

5. Gastrointestinal peptide signalling in health and disease.
   Rozengurt E, Guha S, Sinnett-Smith J.
   Eur J Surg Suppl. 2002;(587):23-38. Review.
   PMID: 16144198 [PubMed - indexed for MEDLINE]

6. IUPHAR Southeast Asian-Western Pacific Region--eighth Meeting. Pharmacology in the Next Millennium. 1-5 November 1999, Taipei, Taiwan.
   Tomlinson B.
   IDrugs. 2000 Feb;3(2):182-4.
   PMID: 16107936 [PubMed]

7. Sphingosine-1-phosphate: an emerging therapeutic target.
   Toman RE, Milstien S, Spiegel S.
   Expert Opin Ther Targets. 2001 Feb;5(1):109-23.
   PMID: 15992170 [PubMed]

8. Therapeutic potential of G-protein coupled receptor kinases in the heart.
   Iaccarino G, Koch WJ.
   Expert Opin Investig Drugs. 1999 May;8(5):545-54.
   PMID: 15992114 [PubMed]

9. Neuropeptide Y receptor antagonists in obesity.
   Gehlert DR, Hipskind PA.
   Expert Opin Investig Drugs. 1997 Dec;6(12):1827-38.
   PMID: 15989583 [PubMed]

10. [G protein-coupled receptors (GPCR), ligand-receptor interaction studies]
    Jasionowski M, Grzonka Z, Lankiewicz L.
    Postepy Biochem. 2000;46(1):60-72. Review. Polish. No abstract available.
    PMID: 15971378 [PubMed - indexed for MEDLINE]

EXHIBIT B

A. Palczewski et al, *Crystal structure of rhodopsin: A G protein-coupled receptor.* Science 2000 289:739-45.

B. Shin N et al, *Molecular modeling and site-specific mutagenesis of the histamine-binding site of the histamine H4 receptor.* Mol Pharmacol. 2002 62:38-47.

C. Chung DA et al, *Mutagenesis and peptide analysis of the DRY motif in the alpha2A adrenergic receptor: evidence for alternate mechanisms in G protein-coupled receptors.* Biochem Biophys Res Commun. 2002 293:1233-41.

D. Mouledous et al, *Functional inactivation of the nociceptin receptor by alanine substitution of glutamine 286 at the C terminus of transmembrane segment VI: evidence from a site-directed mutagenesis study of the ORL1 receptor transmembrane-binding domain.* Mol Pharmacol. 2000 57:495-502.

E. Krasnoperov et al, *Structural requirements for alpha-latrotoxin binding and alpha-latrotoxin-stimulated secretion. A study with calcium-independent receptor of alpha-latrotoxin (CIRL) deletion mutants.* J Biol Chem. 1999 274:3590-6.

F. Hurley et al, *Structure-function studies of the eighth hydrophobic domain of a serotonin receptor.* J Neurochem. 1999 72:413-21

G. Akal-Strader et al, *Residues in the first extracellular loop of a G protein-coupled receptor play a role in signal transduction.* J Biol Chem. 2002 277:30581-90.

H. Yang et al, *Molecular determinants of human melanocortin-4 receptor responsible for antagonist SHU9119 selective activity.* J Biol Chem. 2002 277:20328-35

I. Ulloa-Aguirre et al, *Structure-activity relationships of G protein-coupled receptors.* Arch Med Res. 1999 30:420-35 (Review)

J. Chollet et al, *Biophysical approaches to G protein-coupled receptors: structure, function and dynamic*s. J Comput Aided Mol Des. 1999 13:209-19 (Review)

K. Gimpl et al, *The oxytocin receptor system: structure, function, and regulation.* Physiol Rev. 2001 81:629-83 (Review)

L. Bai et al, *Structure and function of the extracellular calcium-sensing receptor*. Int J Mol Med. 1999 4:115-25 (Review)

M. Olah et al, *The role of receptor structure in determining adenosine receptor activity*. Pharmacol Ther. 2000 85:55-75 (Review)

N. Missale et al, *Dopamine receptors: from structure to function*. Physiol Rev. 1998 78:189-225 (Review)

O. Sealfon et al, *Functional domains of the gonadotropin-releasing hormone receptor.* Cell Mol Neurobiol. 1995 15:25-42 (Review)

P. Filizola et al, *BUNDLE: a program for building the transmembrane domains of G-protein-coupled receptors*. J Comput Aided Mol Des. 1998 12:111-8.

Q. Orry et al, *Modeling and docking the endothelin G-protein-coupled receptor.* Biophys J. 2000 79:3083-94.

R. Califano *SPLASH: structural pattern localization analysis by sequential histograms.*

Bioinformatics. 2000 16:341-57.

S. Gouldson et al, *Domain swapping in G-protein coupled receptor dimers.* Protein Eng. 1998 11:1181-93.

T. Gouldson et al, *Dimerization and domain swapping in G-protein-coupled receptors: a computational study*. Neuropsychopharmacology. 2000 23:S60-77.